which is a divisional application of USSN 07/979638 (now abandoned), filed November 20, 1992, which--.

In the specification at page 1, line 10, after "07/897,778," please insert --(now abandoned)--.

In the Claims

Cancel claims 9, 10, 11, 22, 25-27, 33, 35, and 40.

Amend claims 1-4, 8, 12-15, 17, 18, 21, and 36 as follows.

1. (Amended) [Isolated] An isolated [DNA which is the] *ced-3* [gene] nucleic acid, wherein the polypeptide encoded by said nucleic acid is hydrophilic in nature and has a serine rich region, wherein said nucleic acid has the ability to complement *ced-3* or *ced-4* mutations in an *in vivo* or *in vitro* bioassay.

2. (Amended) [Isolated] The isolated [DNA] *ced-3* nucleic acid sequence of claim 1, comprising [having the nucleotide sequence of Figure 4 (Seq ID # 18)] SEQ ID NO: 18.

3. (Amended) [Isolated] The isolated [DNA encoding] *ced-3* nucleic acid sequence of claim 1, comprising a nucleic acid which encodes the amino acid sequence of [Figure 4

(Seq. ID #19)] SEQ ID NO: 19.

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4. (Amended) [Isolated] An isolated RNA encoded by the [DNA] nucleic acid of ✓ claim 1.

8. (Amended) [Isolated] An isolated [DNA] *ced-3* nucleic acid sequence, wherein

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the polypeptide encoded by said nucleic acid is hydrophilic in nature and has a serine rich region, [which is a mutated *ced-3* or *ced-4* gene having a mutation which] comprising a mutation, wherein said mutation affects [the activity of the gene] the ability of said mutated *ced-3* gene to complement *ced-3* or *ced-4* mutations in an *in vivo* or *in vitro* bioassay.

counter example

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12. (Amended) The [DNA] nucleic acid of claim 8, wherein [the mutated *ced-3* gene] said mutation in *ced-3* is selected from the group consisting of:

a) n1040;

b) n718;

c) n2433;

d) n1164;

e) n717;

f) n1949;

g) n1286;

h) n1129;

i) n1165;

j) n2430;

k) n2426; and

l) n1163

of SEQ ID NO:18.

13. (Amended) The [DNA] nucleic acid of claim 8, wherein [the] said mutation in *ced-3* results in an alteration selected from the group consisting of:

a) a C to T at nucleotide 2310 of SEQ ID NO:18, resulting in a L to F alteration at [codon] position 27 of SEQ ID NO:19;

b) a G to A at nucleotide 2487 of SEQ ID NO:18, resulting in a G to R alteration at [codon] position 65 of SEQ ID NO:19;

c) a G to A at nucleotide 5757 of SEQ ID NO:18, resulting in a G to S alteration at [codon] position 360 of SEQ ID NO:19;

d) a C to T at nucleotide 5940 of SEQ ID NO:18, resulting in a Q to termination alteration at [codon] position 403 of SEQ ID NO: 19;

e) a C to T at nucleotide 6322 of SEQ ID NO:18, resulting in a Q to termination alteration at [codon] position [417] 412 of SEQ ID NO:19;

f) a G to A at nucleotide 6342 of SEQ ID NO:18, resulting in a W to termination alteration at [codon] position 428 of SEQ ID NO:19;

g) a C to T at nucleotide 6434 of SEQ ID NO:18, resulting in a A to V alteration at [codon] position 449 of SEQ ID NO:19;

h) a C to T at nucleotide 6485, resulting in a A to V alteration at [codon] position 466 of SEQ ID NO:19;

i) a G to A at nucleotide 6535, resulting in a E to K alteration at [codon] position 483 of SEQ ID NO:19;

j) a C to T at nucleotide 7020, resulting in an S to F alteration at [codon] position 486 of SEQ ID NO:19;

k) an alteration in mRNA splicing at nucleotide 6297.

14. (Amended) The [DNA] nucleic acid of claim 8, wherein [the] said mutation in *ced-3* is selected from the group consisting of:

a) C to T at nucleotide 2310 of SEQ ID NO: 18;

b) G to A at nucleotide 2487 of SEQ ID NO: 18;

c) G to A at nucleotide 5757 of SEQ ID NO: 18;

d) C to T at nucleotide 5940 of SEQ ID NO: 18;

e) G to A at nucleotide 6297 of SEQ ID NO: 18;

f) C to T at nucleotide 6322 of SEQ ID NO: 18;

g) G to A at nucleotide 6342 of SEQ ID NO: 18;

h) C to T at nucleotide 6434 of SEQ ID NO: 18;

i) C to T at nucleotide 6485 of SEQ ID NO: 18;

j) G to A at nucleotide 6535 of SEQ ID NO: 18;

k) C to T at nucleotide 7020 of SEQ ID NO:18.

15. (Amended) [Isolated] An isolated RNA encoded by the [DNA] nucleic acid of claim 8.

17. (Amended) [Isolated] An isolated [DNA] nucleic acid comprising [which is a gene selected from the group consisting of]:

(a) a [gene] nucleic acid which is structurally related to the *ced-3* [gene] nucleic acid sequence of SEQ ID NO:18, wherein the polypeptide encoded by said nucleic acid is hydrophilic in nature and has a serine rich region;

(b) a [gene] nucleic acid which is functionally related to the *ced-3* [gene] nucleic acid, wherein said functionally related nucleic acid encodes a protein that causes cell death, wherein cell death is measured by the ability of said nucleic acid to complement *ced-3* or *ced-4* mutations in an *in vivo* or *in vitro* bioassay; and

(c) a [gene] nucleic acid which is both structurally and functionally related to the *ced-3* [gene] nucleic acid as described in (a) and (b)[;

(d) a gene which is structurally related to the *ced-4* gene;

(e) a which is functionally related to the *ced-4* gene; and

a5 (f) a gene which is both structurally and functionally related to the *ced-4* gene].

18. (Amended) [Isolated] An isolated RNA encoded by the [DNA] nucleic acid of claim 17. | cont'd dep

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21. (Amended) A probe or primer for identifying a gene which is structurally and functionally related to the *ced-3* [gene] nucleic acid, which belongs to the same family as the *ced-3* nucleic acid, wherein the polypeptide encoded by said nucleic acid sequence is hydrophilic in nature and has a serine rich region, wherein said functionally related nucleic acid encodes a protein that causes cell death, wherein cell death is measured by the ability of said nucleic acid sequence to complement *ced-3* or *ced-4* mutations in an *in vivo* or *in vitro* bioassay, said probe [which is selected from the group consisting of] comprising:

(a) [DNA] nucleic acid [having] comprising all or a portion of the nucleotide sequence of [Figure 4 (Seq. ID # 18)] SEQ ID NO:18;

(b) RNA encoded by the [DNA] nucleic acid of [a)] SEQ ID NO:18;

(c) degenerate oligonucleotides derived from a portion of the amino acid sequence [of] encoded by the nucleic acid of SEQ ID NO:18 [Figure 4 (Seq. ID #19); or

(d) an antibody directed against the protein of c)];

(d) nucleic acid comprising the consensus sequence of a conserved region between at least two other genes which belong to the *ced-3* gene family;

(e) degenerate oligonucleotides derived from the consensus sequence of a conserved region between the proteins encoded by at least two other genes which belong to the *ced-3* gene family; or

(f) RNA encoded by d).

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36. [The isolated DNA of claim 35, wherein the mutation] An isolated nucleic acid sequence comprising a mutation in the *ced-3* gene, wherein said mutation affects the ability of said mutated *ced-3* gene to complement *ced-3* or *ced-4* mutations in an *in vivo* or *in vitro* bioassay, wherein said mutation [has a result selected from the group consisting of] results from:

a) inactivation of the [cell death] *ced-3* gene;

b) constitutive activation of the [cell death] *ced-3* gene; [and] or

c) production of a mutated *ced-3* gene which does not cause cell death and which antagonizes the activity of functioning cell death genes.

Support for the Amendments

The claims have been amended to more precisely define the invention. Support

for the amendments to claims 8, 12-15, 17, 18, 21, and 36 with respect to the functional activity of *ced-3* related nucleic acids, can be found at page 13, lines 20-25 which state,

> "Functionally related genes refer to genes which have similar activity to that of *ced-3* or *ced-4* in that they cause cell death. Such genes can be identified by their ability to complement *ced-3* or *ced-4* mutations in bioassays, as described below."

Such *in vivo* and *in vitro* bioassays are generally described in the specification at page 17, line 15 to page 20, line 4. More specifically, an *in vivo* complementation assay, where *ced-3*(+) DNA capable of complementing the *ced-3* mutant phenotype is identified, is described in Example 2, particularly at page 52, line 11 to page 54, line 24. Support for the amendments to claims 17, 18, and 21, with respect to the structural characteristics of *ced-3*, can be found, for example, at page 11, lines 24-34.

We note here that amendment of claim 13 part (e), where position 417 is deleted and position 412 is added, is supported in Table 3 where position 412 of the *ced-3* gene is the indicated position for this mutation. The original entrance of 417 into claim 13 is believed to be a typographical error. Applicants apologize for this oversight.

REMARKS

Summary of the Office Action

The invention features wild-type and mutant *ced-3* genes and structural and functional equivalents thereof. The *ced-3* gene is required for the onset of programmed